each X is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C(=NH)N(H)Z, C(=O)N(H)Z or OC(=O)N(H)Z;

Z is H or C_1-C_8 alkyl;

[0060] L_1, L_2 and L_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

[0061] Y is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, $O(Q_1)$, halo, $S(Q_1)$, or CN;

each q_1 is, independently, from 2 to 10;

each q_2 is, independently, 0 or 1;

m is 0, 1 or 2;

p is from 1 to 10; and

q_3 is from 1 to 10 with the proviso that when p is 0, q_3 is greater than 1.

[0062] The above 2'-substituents confer a 3'-endo pucker to the sugar where they are incorporated. This pucker conformation further assists in increasing the Tm of the oligonucleotide with its target.

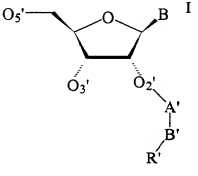
[0063] The high binding affinity resulting from 2' substitution has been partially attributed to the 2' substitution causing a C3' *endo* sugar pucker which in turn may give the oligomer a favorable A-form like geometry. This is a reasonable hypothesis since substitution at the 2' position

by a variety of electronegative groups (such as fluoro and *O*-alkyl chains) has been demonstrated to cause C3' *endo* sugar puckering (De Mesmaeker *et al., Acc. Chem. Res.*, **1995**, *28*, 366-374; Lesnik *et al., Biochemistry*, **1993**, *32*, 7832-7838).

[0064] In addition, for 2'-substituents containing an ethylene glycol motif, a *gauche* interaction between the oxygen atoms around the O-C-C-O torsion of the side chain may have a stabilizing effect on the duplex (Freier *et al.*,Nucleic Acids Research, (1997) 25:4429-4442). Such *gauche* interactions have been observed experimentally for a number of years (Wolfe *et al., Acc. Chem. Res.*, **1972,** *5*, 102; Abe *et al., J. Am. Chem. Soc.*, **1976,** 98, 468). This *gauche* effect may result in a configuration of the side chain that is favorable for duplex formation. The exact nature of this stabilizing configuration has not yet been explained. While we do not want to be bound by theory, it may be that holding the O-C-C-O torsion in a single *gauche* configuration, rather than a more random distribution seen in an alkyl side chain, provides an entropic advantage for duplex formation.

[0065] To better understand the higher RNA affinity of 2'-*O*-methoxyethyl substituted RNA and to examine the conformational properties of the 2'-*O*-methoxyethyl substituent, a self-complementary dodecamer oligonucleotide 2'-*O*-MOE r(CGCGAAUUCGCG) SEQ ID NO: 1 was synthesized, crystallized and its structure at a resolution of 1.7 Ångstrom was determined. The crystallization conditions used were 2 mM oligonucleotide, 50 mM Na Hepes pH 6.2-7.5, 10.50 mM $MgCl_2$, 15% PEG 400. The crystal data showed: space group *C*2, cell constants a=41.2 Å, b=34.4 Å, c=46.6 Å, β=92.4°. The resolution was 1.7 Å at -170°C. The current *R*=factor was 20% (R_{free} 26%).

[0066] This crystal structure is believed to be the first crystal structure of a fully modified RNA oligonucleotide analogue. The duplex adopts an overall A-form conformation and all modified sugars display C3'-*endo* pucker. In most of the 2'-*O*-substituents, the torsion angle around the A'-B' bond, as depicted in Structure II below, of the ethylene glycol linker has a *gauche* conformation. For 2'-O-MOE, A' and B' of Structure II below are methylene moieties of the ethyl portion of the MOE and R' is the methoxy portion.



II

[0067] In the crystal, the 2'-O-MOE RNA duplex adopts a general orientation such that the crystallographic 2-fold rotation axis does not coincide with the molecular 2-fold rotation axis. The duplex adopts the expected A-type geometry and all of the 24 2'-O-MOE substituents were visible in the electron density maps at full resolution. The electron density maps as well as the temperature